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PTO/SB/05 (4/98)

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**UTILITY  
PATENT APPLICATION  
TRANSMITTAL**

Attorney Docket No. 1195-003

First Inventor or Application Identifier GUARNA, Antonio

Title BENZOIC QUINOLIZINE DERIVATIVES  
AND THEIR USE AS 5-ALPHA...

Express Mail Label No. EL548492206US

(Only for new nonprovisional applications under 37 C.F.R. § 1.53(b))

**APPLICATION ELEMENTS**

See MPEP chapter 600 concerning utility patent application contents.

1. ☐ \* Fee Transmittal Form (e.g., PTO/SB/17)  
(Submit an original and a duplicate for fee processing)
2. ☒ Specification [Total Pages 33]  
(preferred arrangement set forth below)
- Descriptive title of the invention
  - Cross References to Related Applications
  - Statement Regarding Fed sponsored R & D
  - Reference to Microfiche Appendix
  - Background of the invention
  - Brief Summary of the invention
  - Brief Description of the Drawings (if filed)
  - Detailed Description
  - Claim(s)
  - Abstract of the Disclosure
3. ☐ Drawing(s) (35 U.S.C. 113) [Total Sheets ]
4. Oath or Declaration [Total Pages ]
- a. ☐ Newly executed (original or copy)
- b. ☐ Copy from a prior application (37 C.F.R. § 1.63(d))  
(for continuation/divisional with Box 16 completed)
1. ☐ DELETION OF INVENTOR(S)  
Signed statement attached deleting  
inventor(s) named in the prior application,  
see 37 C.F.R. §§ 1.63(d)(2) and 1.33(b).

\* NOTE FOR ITEMS 1 & 13: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY  
FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT  
IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28).

ADDRESS TO: Assistant Commissioner for Patents  
Box Patent Application  
Washington, DC 20231

5. ☐ Microfiche Computer Program (Appendix)
6. Nucleotide and/or Amino Acid Sequence Submission  
(if applicable, all necessary)
- a. ☐ Computer Readable Copy
- b. ☐ Paper Copy (identical to computer copy)
- c. ☐ Statement verifying identity of above copies

**ACCOMPANYING APPLICATION PARTS**

7. ☐ Assignment Papers (cover sheet & document(s))
8. ☐ 37 C.F.R. § 3.73(b) Statement ☐ Power of  
(when there is an assignee) Attorney
9. ☐ English Translation Document (if applicable)
10. ☐ Information Disclosure ☐ Copies of IDS  
Statement (IDS)/PTO-1449 Citations
11. ☐ Preliminary Amendment
12. ☒ Return Receipt Postcard (MPEP 503)  
(Should be specifically itemized)
13. ☐ \* Small Entity ☐ Statement filed in prior application,  
Statement(s) Status still proper and desired  
(PTO/SB/09-12)
14. ☐ Certified Copy of Priority Document(s)  
(if foreign priority is claimed)
15. ☒ Other: Copies of Int'l. Search  
Rpt., Int'l. Prel.  
Exam. Rpt.

16. If a CONTINUING APPLICATION, check appropriate box, and supply the requisite information below and in a preliminary amendment:

☐ Continuation ☐ Divisional ☒ Continuation-in-part (CIP) of prior application No: PCT / EP98/08582

Prior application information Examiner Group / Art Unit:

For CONTINUATION or DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 4b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

**17. CORRESPONDENCE ADDRESS**

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Signature		Date	6/13/00

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Box Patent Application, Washington, DC 20231.

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[illegible]

In re Application of:

Group Art Unit:

Examiner:

New York, NY 10036  
June 13, 2000

**PRELIMINARY AMENDMENT**

Kindly amend the subject application as follows:

Kindly amend the specification as follows:

Page 1, after the title and before line 1, please insert:

--The present application is a continuation-in-part of and claims priority to International Application No. PCT/EP98/08582, filed December 21, 1998 and European Application No. EP 97122733.5 filed December 23, 1997.--

REMARKS

The specification has been amended to indicate that the present application is a continuation-in-part of International Application No. PCT/EP98/08582, filed December 21, 1998.

Respectfully submitted,



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Registration No. 25,669

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
PATENT OPERATION

INVENTORS:

Antonio Guarna

and

Mario Serio

TITLE:

BENZO[C]QUINOLIZINE DERIVATIVES AND THEIR USE AS 5 ALPHA  
REDUCTASE INHIBITORS

CORRESPONDENCE ADDRESS:

James V. Costigan  
Registration No. 25,669

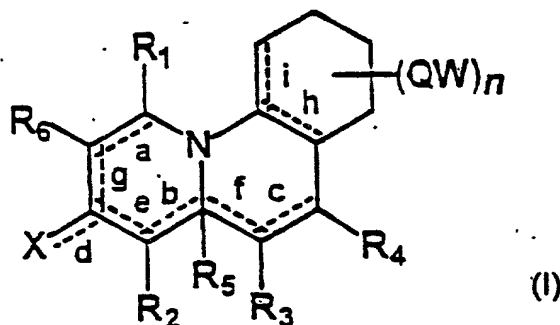
HEDMAN, GIBSON & COSTIGAN, P.C.  
1185 Avenue of the Americas  
New York, NY 10036  
(212) 302-8989

**Benzo[c]quinolizine derivatives and their use as 5 $\alpha$ -reductases inhibitors.**

The present invention refers to fully and partially saturated benzo[c]-quinolizine derivatives of general formula (I) their pharmaceutically acceptable salts or esters, processes for their preparation and composition for pharmaceutical and agricultural use containing them.

**Field of the invention**

The present invention refers to benzo[c]quinolizine derivatives of general formula (I)



wherein:

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>6</sub>, same or different, are chosen in the group consisting of: H, C<sub>1-8</sub>alkyl, C<sub>2-8</sub>alkenyl, C<sub>2-8</sub>alkynyl, cycloalkyl, aryl, heterocycle, halogen, CN, azide, NRR', C<sub>1-8</sub>alkylamino, arylamino, C<sub>1-8</sub>alkyloxy, aryloxy, COOR, CONRR', C(=O)R wherein R and R', same or different, are chosen in the group consisting of: H, C<sub>1-8</sub>alkyl, cycloalkyl, aryl, heterocycle, arylC<sub>1-8</sub>alkyl;

R<sub>5</sub> is chosen in the group consisting of: H, C<sub>1-8</sub>alkyl, C<sub>1-8</sub>alkylaryl, COOR, CN, aryl, heterocycle, C<sub>1-8</sub>alkyl-heterocycle; C<sub>1-8</sub>alkyl-heterocycle-ribose-phosphate

X is chosen in the group consisting of: O, C(=O)R, COOR, NO<sub>2</sub>, CONR'R wherein R and R' are as above defined;

Q is chosen in the group consisting of: simple bond, C<sub>1-8</sub>alkyl, C<sub>2-8</sub>alkenyl, C<sub>2-8</sub>alkynyl, cycloalkyl, CO, CONR, NR, wherein R is as above defined;

W is chosen in the group consisting of: H, C<sub>1-8</sub>alkyl, C<sub>2-8</sub>alkenyl, C<sub>2-8</sub>alkynyl, cycloalkyl, trifluoromethyl, C<sub>1-8</sub>alkoxy, C<sub>1-8</sub>alkoxy-C<sub>1-8</sub>alkyl, arylC<sub>1-8</sub>alkyl, aryl, aryloxy, arylamino, C<sub>1-8</sub>alkylcarbonyl, arylcarbonyl, arylcarboxyl, arylcarboxamide, halogen, CN, NRR', C<sub>1-8</sub>alkylamino, heterocycle wherein the groups alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocycle, can be substituted; n is an integer comprised between 1 and 4;

the symbol ---- means that the corresponding bonds a, b, c, d e, f, g, h and i can be a simple or a double bond; with the proviso that when b or f are a double bond then the group  $R_5$  is absent;

their pharmaceutically acceptable salts or esters, their process of preparation and their use as inhibitors of steroid  $5\alpha$ -reductases.

#### State of the art

The enzyme known as steroid  $5\alpha$ -reductase (hereinafter indicated as  $5\alpha$ -reductase) is a system formed by two iso-enzymes (type I and type II or  $5\alpha$ R-I and  $5\alpha$ R-II respectively) which converts testosterone into dihydrotestosterone, the most powerful androgen circulating in the body. The type I iso-enzyme ( $5\alpha$ R-I) is mainly present in liver and skin while the type II iso-enzyme ( $5\alpha$ R-II) is mainly present in the prostate tissue and in the male sexual organs and its activity is essential in the fetal developing process for the differentiation of the external sexual organs. The production of dihydrotestosterone is associated with some pathologies which are widely diffused as for example benign prostate hypertrophy, prostate cancer, baldness and acne in men and hirsutism in women. More particularly iso-enzyme I plays a role in the pathologies regarding the skin while iso-enzyme-II is involved in prostate pathologies. In the recent years a lot of international searchers have tried to isolate new compounds capable of inhibiting the  $5\alpha$ -reductase enzyme in order to treat the above said pathologies, especially, if possible, acting selectively on only one of the two iso-enzymes. Inhibitors of  $5\alpha$ -reductase, and also of the iso-enzymes  $5\alpha$ R-I and  $5\alpha$ R-II were already described [see for example J.Med.Chem. 36, 4313-15 (1993), J.Med.Chem. 37, 3871-74 (1994), J.Med.Chem. 40, 1112 (1997) J.Med.Chem. 40, 3466 (1997)]; for example finasteride was used with success in the treatment of benign prostate hypertrophy.

In EP-703 221, EP-591 582, EP-591 583, EP-532 190 and EP-531 026 benzoquinoline-3-ones as  $5\alpha$ -reductase inhibitors are reported while WO 94/21614 describes substituted 3-phenanthridinone derivatives having the same action.

2a

Journal of the Chemical Society, Perkin Transaction 1, vol 3, 1979 pages 584 – 590, describes i.a. a benzo[c]quinolizine (see compound 8), without indicating any use thereof.

It is therefore evident the importance of developping new compounds capable of inhibiting the action of the 5 $\alpha$ -reductase enzyme and in particular capable of acting selectively on 5 $\alpha$ R-I iso-enzyme which, as said, is responsible, of widely diffused pathologies having an high impact as baldness in men and hirsutism in women.

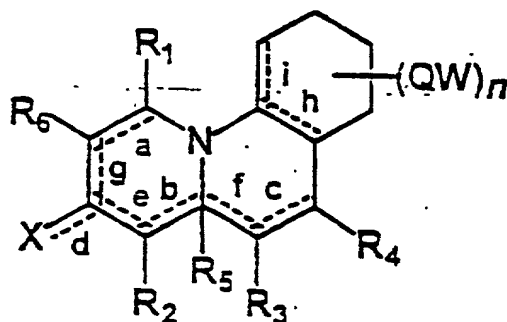
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Therefore the invention refers also to a method for the treatment of pathologies related to  $5\alpha$ -reductase enzymes and in particular for the treatment of acne, baldness, prostatic cancer and prostatic hypertrophy in men and hirsutism in women. Moreover it was also found, and it is another object of the present invention, that the compound of formula (I) can inhibit steroid  $5\alpha$ -reductase enzymes in plants and therefore can selectively regulate the plant growth in light and dark conditions. The compounds according to the present invention can be used as phyto-pharmaceuticals in agriculture permitting to improve the morphogenesis and development of commercially useful plants or as herbicides capable of inhibiting the growth of infesting plants. The compounds can therefore be used in agricultural compositions for regulating the plant growth in particular those which are distributed on the seeds and/or the plants to treat.

#### Detailed description of the invention

The present invention refers to new compounds capable of inhibiting the  $5\alpha$ -reductase enzyme, either selectively in respect of  $5\alpha$ R-I and  $5\alpha$ R-II or on both the iso-enzymes, useful for the treatment of the pathologies mediated by the enzyme or for agricultural uses as plant growth regulators or herbicides.

The products according to the invention have general formula



(I)

wherein the substituents  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $X$ ,  $Q$ ,  $W$ ,  $n$  and the symbol  $---$  are as above defined.

According to the present invention with group  $C_{1-8}$ alkyl,  $C_{2-8}$  alkenyl and  $C_{2-8}$ alkynyl are indicated linear or branched alkyl radicals as for example: methyl,





Heterocycle means in particular: saturated or aromatic heterocycles containing one or more N atoms, more particularly: pyridine, imidazole, pyrrole, indole, triazoles, pyrrolidine, piperidine.

Phosphate means the anion of mono-, di- or triphosphoric acid

5 Halogen means: fluorine, chlorine, bromine, iodine.

The substituents of the above said group W are preferably: halogen, OR, phenyl, NRR', CN, COOR, CONRR', C<sub>1-8</sub>alkyl (wherein R and R' are as above defined).

10 In particular, according to the present invention compounds of formula (I) are preferred wherein:

R<sub>5</sub> = H, C<sub>1-8</sub>alkylaryl, COOR, CN, aryl, heterocycle, C<sub>1-8</sub>alkyl-heterocycle; or a group C<sub>1-8</sub>alkyl-heterocycle-ribose-phosphate

X = O, COOH

15 Q = simple bond, CO, CONR, NR (wherein R is as above defined) W = H, F, Cl, Br, Me, t-butyl, C<sub>1-8</sub>alkoxy, 2,5-dimethylhexyl, trifluoromethyl, 2,5-(di-trifluoromethyl)-phenyl, 4-methoxy-phenyl, 4-fluoro-phenyl, phenyl, phenyl-C<sub>1-8</sub>alkyl, C<sub>1-8</sub>alkylcarbonyl, phenylcarbonyl.

n = 1 and 2

20 R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>6</sub> = H, Me, CN, phenyl, COOR, CONRR' (wherein R and R' are as above defined). Among the pharmaceutically acceptable esters and salts according to the present invention the following can be mentioned: hydrochloride, sulphate, citrate, formiate, phosphate.

Preferred compounds according to the present invention are:

25 2,3,4,4a,5,6,6a,7,8,9,10,10a-dodecahydro-(1H)-benzo[c]quinolizin-3-one;  
8-chloro-2,3,4,4a,5,6,6a,7,8,9,10,10a-dodecahydro-(1H)-benzo[c]quinolizin-3-one;  
2,3,4,4a,5,6,6a,7,8,9,10,10a-dodecahydro-8-methyl-(1H)-benzo[c]quinolizin-3-one;  
2,3,4,4a,5,6,6a,7,8,9,10,10a-dodecahydro-4-methyl-(1H)-benzo[c]quinolizin-3-  
30 one;  
2,3,4,4a,5,6,6a,7,8,9,10,10a-dodecahydro-1-methyl-(1H)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-(1*H*)-benzo[c]quinolizin-3-one;  
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-(1*H*)-benzo[c]quinolizin-3-one;  
2,3,5,6,6a,7,8,9,10,10a-decahydro-8-methyl-(1*H*)-benzo[c]quinolizin-3-one;  
2,3,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-(1*H*)-benzo[c]quinolizin-3-one;  
5 2,3,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-(1*H*)-benzo[c]quinolizin-3-one;  
(4a $\alpha$ ,6a $\beta$ ,10a $\alpha$ )-3,4,5,6,6a,7,8,9,10,10a-decahydro-(4a*H*)-benzo[c]quinolizin-3-one ;  
(4a $\beta$ ,6a $\beta$ ,10a $\alpha$ )-3,4,5,6,6a,7,8,9,10,10a-decahydro-(4a*H*)-benzo[c]quinolizin-3-one ;  
10 3,4,5,6,6a,7,8,9,10,10a-decahydro-(4a*H*)-benzo[c]quinolizin-3-one;  
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-(4a*H*)-benzo[c]quinolizin-3-one;  
3,4,5,6,6a,7,8,9,10,10a-decahydro-8-methyl-(4a*H*)-benzo[c]quinolizin-3-one;  
3,4,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-(4a*H*)-benzo[c]quinolizin-3-one;  
3,4,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-(4a*H*)-benzo[c]quinolizin-3-one;  
15 8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-(1*H*)-benzo[c]quinolizin-3-one;  
2,3,5,6,6a,7,8,9,10,10a-decahydro-4,8-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;  
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-(1*H*)-benzo[c]quinolizin-3-one;  
20 2,3,5,6,6a,7,8,9,10,10a-decahydro-1,4-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;  
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-(4a*H*)-benzo[c]quinolizin-3-one;  
3,4,5,6,6a,7,8,9,10,10a-decahydro-4,8-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;  
25 8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-(4a*H*)-benzo[c]quinolizin-3-one;  
3,4,5,6,6a,7,8,9,10,10a-decahydro-1,8-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;  
2,3,5,6,6a,7,8,9,10,10a-decahydro-5-methyl-(1*H*)-benzo[c]quinolizin-3-one;  
30 8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-5-methyl-(1*H*)-benzo[c]quinolizin-3-one;  
2,3,5,6,6a,7,8,9,10,10a-decahydro-5,8-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-4,5-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;  
2,3,5,6,6a,7,8,9,10,10a-decahydro-1,5-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;  
3,4,5,6,6a,7,8,9,10,10a-decahydro-5-methyl-(4a*H*)-benzo[c]quinolizin-3-one;  
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-5-methyl-(4a*H*)-benzo[c]quinolizin-

5 3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-5,8-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

10 3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-4,5-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-4,5,8-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;

15

8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-1,5-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-1,4,5-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;

20

8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5,8-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5-dimethyl-(4a*H*)-

25

benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5,8-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-6-methyl-(1*H*)-benzo[c]quinolizin-3-one;

8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-6-methyl-(1*H*)-benzo[c]quinolizin-3-

30

one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-6,8-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-4,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-1,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;  
3,4,5,6,6a,7,8,9,10,10a-decahydro-6-methyl-(4a*H*)-benzo[c]quinolizin-3-one;  
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-6-methyl-(4a*H*)-benzo[c]quinolizin-3-one;

5 3,4,5,6,6a,7,8,9,10,10a-decahydro-6,8-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-4,6-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-1,6-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

10 8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-4,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-4,6,8-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;

15 8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-1,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-1,4,6-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;

8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-4,6-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

20 3,4,5,6,6a,7,8,9,10,10a-decahydro-4,6,8-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-1,6-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

25 3,4,5,6,6a,7,8,9,10,10a-decahydro-1,6,8-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-5,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-5,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

30 2,3,5,6,6a,7,8,9,10,10a-decahydro-5,6,8-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-4,5,6-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-1,5,6-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-5,6-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-5,6-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-5,6,8-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5,6-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5,6-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-4,5,6-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-4,5,6,8-tetramethyl-(1*H*)-benzo[c]quinolizin-3-one;

8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-1,5,6-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-1,4,5,6-tetramethyl-(1*H*)-benzo[c]quinolizin-3-one;

8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5,6-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5,6,8-tetramethyl-(4a*H*)-benzo[c]quinolizin-3-one;

8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5,6-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5,6,8-tetramethyl-(4a*H*)-

benzo[c]quinolizin-3-one;

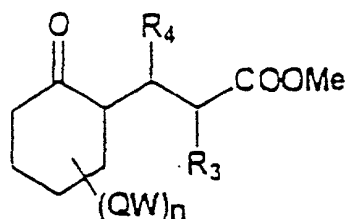
5,6,6a,7,8,9,10,10a-octahydro-(3*H*)-benzo[c]quinolizin-3-one;

8-chloro-5,6,6a,7,8,9,10,10a-octahydro-(3*H*)-benzo[c]quinolizin-3-one;

- 5,6,6a,7,8,9,10,10a-octahydro-8-methyl-(3*H*)-benzo[c]quinolizin-3-one;  
 5,6,6a,7,8,9,10,10a-octahydro-4-methyl-(3*H*)-benzo[c]quinolizin-3-one;  
 8-chloro-5,6,6a,7,8,9,10,10a-octahydro-4-methyl-(3*H*)-benzo[c]quinolizin-3-one;  
 5,6,6a,7,8,9,10,10a-octahydro-4,8-dimethyl-(3*H*)-benzo[c]quinolizin-3-one;  
 5 2,3,5,6,7,8,9,10-octahydro-(1*H*)-benzo[c]quinolizin-3-one;  
 8-chloro-2,3,5,6,7,8,9,10-octahydro-(1*H*)-benzo[c]quinolizin-3-one;  
 2,3,5,6,7,8,9,10-octahydro-8-methyl-(1*H*)-benzo[c]quinolizin-3-one;  
 2,3,5,6,6a,7,8,9-octahydro-(1*H*)-benzo[c]quinolizin-3-one;  
 8-chloro-2,3,5,6,6a,7,8,9-octahydro-(1*H*)-benzo[c]quinolizin-3-one;  
 10 2,3,5,6,6a,7,8,9-octahydro-8-methyl-(1*H*)-benzo[c]quinolizin-3-one;  
 4a-benzyl-3,4,5,6,6a,7,8,9,10,10a-decahydro-(4a*H*)-benzo[c]quinolizin-3-one;  
 4a-benzyl-8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-(4a*H*)-  
 benzo[c]quinolizin-3-one;  
 4a-benzyl-3,4,5,6,6a,7,8,9,10,10a-decahydro-8-methyl-(4a*H*)-  
 15 benzo[c]quinolizin-3-one;  
 4a-benzyl-3,4,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-(4a*H*)-  
 benzo[c]quinolizin-3-one;  
 4a-benzyl-3,4,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-(4a*H*)-  
 benzo[c]quinolizin-3-one;  
 20 3,4,5,6,6a,7,8,9,10,10a-decahydro-4a-(4-pyridyl)methyl-(4a*H*)-  
 benzo[c]quinolizin-3-one;  
 8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-4a-(4-pyridyl)methyl-(4a*H*)-  
 benzo[c]quinolizin-3-one;  
 3,4,5,6,6a,7,8,9,10,10a-decahydro-8-methyl-4a-(4-pyridyl)methyl-(4a*H*)-  
 25 benzo[c]quinolizin-3-one;  
 3,4,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-4a-(4-pyridyl)methyl-(4a*H*)-  
 benzo[c]quinolizin-3-one;  
 3,4,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-4a-(4-pyridyl)methyl-(4a*H*)-  
 benzo[c]quinolizin-3-one;  
 30 Dodecahydro-benzo[c]quinolizin-3-ones and decahydro-benzo[c]quinolizin-3-  
ones according to the present invention, wherein the double bonds i and h are  
 absent, can be prepared as shown in Scheme 1, according to the general

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preparation of benzo[c]quinolizine-3-ones already reported in the patent WO 97/29107; in particular, for example, starting from compounds of formula 2



wherein  $R_3$ ,  $R_4$ , W, Q and n are as above defined.

The compounds 2 are commercially available or can be prepared according to known techniques.

As it can be seen from the Scheme 1 the preparation of the compounds according to the invention involves the cyclization of the ester 2 to the enamide 3 by heating at 120°C compounds 2 in formic acid in the presence of ammonium hydrogencarbonate. The enamide 3 is reduced to the *trans*-fused amide 4 for example with sodiumcyanoborohydride at pH 4, followed by the protection of the amide-group with a protecting group, for example tert-butoxycarbonyl (t-Boc), to give compound 5; compound 5 is reduced to compound 6, for example (when  $R_5$  is H) with sodium borohydride in ethanol (pH 4), particularly good yields are obtained when the reduction is performed with  $\text{LiEt}_3\text{BH}$  in THF at -78°C, followed by addition of HCl 2N anhydrous solution in ethanol up to pH 4. The so obtained compound 6 is thereafter reacted with a silyloxydiene 8, produced "in situ" starting from vinyl-ketones 7 (wherein  $R_1$ ,  $R_2$  and  $R_6$  are as above defined) with a silylating agent as trimethylsilyltrifluorometansulphonic anhydride (TMSOTf) and thereafter hydrolyzed, for example in sodium hydrogencarbonate, to give the compounds of formula (I) wherein  $X = \text{O}$ . The possible introduction of the double bonds and the transformation of the group X in one of the other groups mentioned above can be easily performed according to known techniques starting from the corresponding compound of formula (I) obtained as indicated. For example the introduction of the double bonds in position a or/and b, can be performed by



reaction of dichlorodicyanoquinone (DDQ) with the corresponding silylenolethers or by oxidation with mercuric acetate of the saturated corresponding compound obtained as described above.

According to a different embodiment of the present invention it is possible to obtain directly the double bond in position "a" by performing the reaction between products 6 and 8 (wherein  $R_1$  is  $OCH_3$  and  $R_2$  and  $R_6$  are H) in the presence of  $TiCl_4$  or TMSOTf as Lewis acids (product 8 as above defined is in this case a commercially available product): Acting in this way it is also possible to direct the stereochemical outcome of the hydrogen atom in position 4a ( $R_5 = H$ ) in the final compound. In particular when using  $TiCl_4$  the compound, wherein the above said hydrogen atom is on the same side of the hydrogen in position 10a, is obtained while using TMSOTf the above said hydrogen atom is on the opposite side on respect to the hydrogen in position 10a.

The transformation of group X can be performed via the corresponding enoltriflates and their carbonylation in the presence of palladium diacetate, triphenylphosphine and the suitable nucleophilic reagent (alcohol, amine, nitro-group).

The compounds according to the present invention wherein the double bonds i or h and b are present, can be prepared as shown in Scheme 2, for example starting from the above said compounds of formula 2.

The key step of the process is the thermal rearrangement-cyclization of the isoxazoline-5-spirocyclopropane 14 to final product 1. This process has been already applied for the synthesis of other nitrogen bridgehead polycyclic compounds as reported in *J. Org. Chem.* 1988, 53, 2426 and in *J. Med. Chem.* 1997, 40, 1112.

As it can be seen from the Scheme 2 the preparation of the compounds according to the invention involves protection of the carbonyl of compound 2 (wherein  $R_3$  and  $R_4$  are as above defined) as a ketal, for example with ethylenglicole under acid catalysis, followed by the selective reduction of the ester group in compound 9 to aldehyde 10, for example by DIBAL at  $-78^\circ C$ . The transformation of the aldehyde 10 to oxime 11, made for example by

reaction with hydroxylamine hydrochloride in pyridine, is followed by cycloaddition to methylenecyclopropane 12 (wherein  $R_1$ ,  $R_2$ ,  $R_6$  are as above defined) of the *in situ* generated nitrile oxide by reaction of oxime 11 with sodium hypochlorite and triethylamine. The isoxazoline-5-spirocyclopropane 13 is then deprotected under acid catalysis and submitted to thermal rearrangement in boiling DMF for 3-6 hrs to give compounds 1.

Octahydrobenzo[c]quinolizin-3-ones of formula 1, wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_6$  are H, QW is H or  $-\text{CH}_2\text{CONH}t\text{Bu}$  (at position 8),  $n = 1$  and both the double bonds b and h (or i) are present can be prepared for example starting from compound 2 wherein  $R_3$ ,  $R_4$ , are H and QW is H or 5-(*N*-*t*-butyl)acetamido and  $n = 1$ .

#### Example 1

Preparation of methyl 3-[2-(1,3-dioxolan-2-yl)cyclohexyl]propanoate.

[compound 9 wherein  $(\text{QW})_n = \text{H}$ ,  $R_3 = R_4 = \text{H}$ ]

In a flask provided with a Dean-Stark apparatus, methyl ester 2 (20.0 g, 109 mmol), ethylenic glycol (60 mL, 1.08 mol) and *p*-TsOH (0.8 g, 5 mmol) were dissolved in toluene (550 mL) and the resulting solution was heated under reflux. After 4 h the reaction was complete and the mixture was washed with  $\text{NaHCO}_3$  2 N, water and dried over  $\text{Na}_2\text{SO}_4$ . After filtration and evaporation of the solvent, a crude yellow oil was obtained. This was purified by distillation under reduced pressure, affording pure 9 [15.9 g, 64%, bp 127-130 °C (2 mbar)].

#### Example 2

Preparation of 3-[2-(1,3-dioxolan-2-yl)cyclohexyl]propanal [compound 10 wherein  $(\text{QW})_n = \text{H}$ ,  $R_3 = R_4 = \text{H}$ ]

To a solution of 9 (15.7 g, 69.1 mmol) in toluene (220 mL) cooled at -78 °C, DIBAL-H (1.2 M solution in toluene, 116 mL, 135 mmol) was slowly added during 3 h. After 3 h of stirring, the mixture was poured into water (110 mL) and allowed to warm to room temperature. After filtration on a Celite layer, the organic phase was dried over  $\text{Na}_2\text{SO}_4$ . After filtration and evaporation of the solvent the residual crude oil was purified by chromatography (petroleum ether-EtOAc, 2:1,  $R_f$  0.30), affording pure aldehyde 10 as oil (6.6 g, 48%).

Example 3.

Preparation of 3-[2-(1,3-dioxolan-2-yl)cyclohexyl]propanal oxime [compound 11 wherein  $(QW)_n = H$ ,  $R_3 = R_4 = H$ ].

A solution of aldehyde 10 (6.12 g, 31.0 mmol) and  $NH_2OH \cdot HCl$  (2.76 g, 40.0 mmol) in pyridine (120 mL) was stirred for 2 h at room temperature. The mixture was extracted with  $Et_2O$  and the organic layer washed with water and dried over  $Na_2SO_4$ . After filtration and evaporation of the solvent the crude oil obtained was purified by chromatography (petroleum ether-  $EtOAc$ , 1.5:1,  $R_f$  0.5). Recrystallization from  $Et_2O$ -petroleum ether gave pure oxime 11 (4.02 g, 61%, mp 74-75 °C) as a 1:1 mixture of E,Z diastereoisomers.

Example 4

Preparation of 6-[2-[2-(1,3-dioxolan-2-yl)cyclohexyl]ethyl]-4-oxa-5-azaspiro[2.4]hept-5-ene [compound 13 wherein  $(QW)_n = H$ ,  $R_1 = R_2 = R_3 = R_4 = R_6 = H$ ].

Liquid methylenecyclopropane [compound 12 wherein  $R_1 = R_2 = R_6 = H$ ] (5 mL) was transferred by a double-tipped needle into a solution of oxime 11 (4.02 g, 18.8 mmol) and  $Et_3N$  (226 mg, 2.23 mmol) in  $CH_2Cl_2$  (35 mL) cooled at -60 °C. The mixture was allowed to warm to 0 °C and  $NaClO$  (8% solution, 54 mL) was slowly added in 3.5 h. The solution was stirred for 21 h, then the phases were separated, the aqueous layer was extracted with  $CH_2Cl_2$  (3 x 25 mL) and the combined organic layers were dried over  $Na_2SO_4$ . After filtration and evaporation of the solvent, crude 13 (4.89 g, 73%) was obtained and used without purification in the next reaction.

Example 5

Preparation of 6-[2-(2-oxocyclohexyl)ethyl]-4-oxa-5-azaspiro[2.4]hept-5-ene [compound 14 wherein  $(QW)_n = H$ ,  $R_1 = R_2 = R_3 = R_4 = R_6 = H$ ].

Isoxazoline 13 (3.64 g, 13.7 mmol) and *p*-TsOH (392 mg, 2.23 mmol) were dissolved in acetone (90 mL) and water (30 mL) and the resulting solution was stirred at room temperature for 7 days. The product was extracted with  $CH_2Cl_2$ , the organic phase washed with  $NaHCO_3$  (2 N) and dried over  $Na_2SO_4$ . After filtration and evaporation of the solvent, a yellow crude oil (2.36 g) was obtained. This was purified first by chromatography ( $CH_2Cl_2$ - $EtOAc$ , 12.5:1,  $R_f$

0.35) and then by recrystallization from Et<sub>2</sub>O-petroleum ether, affording pure isoxazoline 14 (1.43 g, 47%, mp 109 °C).

#### Example 6

Preparation of 2,3,5,6,7,8,9,10-octahydro-(1*H*)-benzo[c]quinolizin-3-one [compound 1 wherein (QW)<sub>n</sub> = H, R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = R<sub>6</sub> = H and h = double bond].

and 2,3,5,6,6a,7,8,9-octahydro-(3*H*)-benzo[c]quinolizin-3-one [compound 1 wherein (QW)<sub>n</sub> = H, R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = R<sub>6</sub> = H and i = double bond].

Isoxazoline 14 (476 mg, 2.15 mmol) dissolved in dry DMF (50 mL) was heated under reflux for 3 h. After distillation of the solvent, a yellow crude oil (470 mg) was obtained, containing a mixture of rearrangement products. This oil was purified by chromatography (CH<sub>2</sub>Cl<sub>2</sub>-MeOH, 20:1), affording pure 1 (163 mg, 37%, R<sub>f</sub> 0.36, oil) as 10:1 mixture of the two isomers having the double bond in position h or i respectively.

#### Example 7

Preparation of methyl 3-[[2-(1,3-dioxolan-2-yl)-5-(*N*-*t*-butyl)acetamido]cyclohexyl]]propanoate [compound 9 wherein (QW)= 5-(*N*-*t*-butyl)acetamido n = 1, R<sub>3</sub> = R<sub>4</sub> = H]

Prepared as in example 1. Starting from compound 2 [wherein (QW)= 5-(*N*-*t*-butyl)acetamido n = 1, R<sub>3</sub> = R<sub>4</sub> = H] (32.14 g, 108 mmol), crude ketal 9 (22.2 g, 60%) was obtained as an oil. A portion (100 mg) of this crude oil was purified by chromatography (CH<sub>2</sub>Cl<sub>2</sub>-MeOH, 30:1, 1% Et<sub>3</sub>N, R<sub>f</sub> 0.31, oil), affording 9 as a mixture of *cis* and *trans* isomers.

#### Example 8

Preparation of 3-[[2-(1,3-dioxolan-2-yl)-5-(*N*-*t*-butyl)acetamido]cyclohexyl]]-propanal oxime [compound 11 wherein (QW)= 5-(*N*-*t*-butyl)acetamido n = 1, R<sub>3</sub> = R<sub>4</sub> = H]

A solution of ketal [compound 9 wherein (QW)= 5-(*N*-*t*-butyl)acetamido n = 1, R<sub>3</sub> = R<sub>4</sub> = H] (22.1 g, 64.7 mmol) in toluene (500 mL) was cooled at -78 °C; DIBAL-H (solution 1 M in toluene, 288 mL) was then slowly added in 4 h and the resulting solution was stirred for 3 h. After addition of water (260 mL), the mixture was allowed to warm to room temperature, extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 x

200 mL) and the organic layer dried over  $\text{Na}_2\text{SO}_4$ . After filtration and evaporation of the solvent a crude oil (17.2 g) was obtained, used without purification for the next step.

Then, under stirring, to a solution of distilled oxalyl chloride (10.9 mL, 125 mmol) in  $\text{CH}_2\text{Cl}_2$  (270 mL), cooled at  $-60^\circ\text{C}$ , DMSO (15 mL, 211 mmol) was added, followed by slow addition (25 min) of a solution of the above crude oil in  $\text{CH}_2\text{Cl}_2$  (260 mL). After 15 min,  $\text{Et}_3\text{N}$  (56 mL) was slowly added in 15 min. After 5 min stirring, the mixture was warmed to room temperature and washed with water (535 mL); after separation of the phases, the aqueous one was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 250 mL) and the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ . After filtration and evaporation of the solvent, the aldehyde [compound 10 wherein (QW)= 5-(*N*-*t*-butyl)acetamido  $n = 1$ ,  $R_3 = R_4 = \text{H}$ ] was obtained as a crude oil (14.6 g), used without purification for the next reaction.

A solution of this aldehyde (14.6 g) in pyridine (210 mL) was added to a solution of  $\text{NH}_2\text{OH}\cdot\text{HCl}$  (13.7 g, 196.9 mmol) in pyridine (107 mL) and the resulting mixture was stirred at room temperature for 20 h. The mixture was poured into  $\text{CH}_2\text{Cl}_2$  (800 mL) and washed with water; after separation of the phases, the aqueous one was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 200 mL) and the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ . After filtration and evaporation of the solvent, crude oxime [compound 11 wherein (QW)= 5-(*N*-*t*-butyl)acetamido  $n = 1$ ,  $R_3 = R_4 = \text{H}$ ] (11.3 g) was obtained. This was purified by chromatography eluting with  $\text{CHCl}_3$ -MeOH, 50:1, 1%  $\text{Et}_3\text{N}$ , and then with  $\text{CHCl}_3$ -MeOH, 3:1, 1%  $\text{Et}_3\text{N}$  ( $R_f$  0.32), affording pure oxime [compound 11 wherein (QW)= 5-(*N*-*t*-butyl)acetamido  $n = 1$ ,  $R_3 = R_4 = \text{H}$ ] (7.41 g, 35%, oil) as a 1:1 mixture of *E/Z* diastereoisomers

#### Example 9

Preparation of 6-[2-[2-(1,3-dioxolan-2-yl)-5-(*N*-*t*-butyl)acetamido]cyclohexyl]ethyl]-4-oxa-5-azaspiro[2.4]hept-5-ene [compound 13 wherein (QW)= 5-(*N*-*t*-butyl)acetamido  $n = 1$ ,  $R_1 = R_2 = R_3 = R_4 = R_6 = \text{H}$ ]

Prepared as example 4. Starting from the above prepared oxime [compound 11 wherein (QW)= 5-(*N*-*t*-butyl)acetamido  $n = 1$ ,  $R_3 = R_4 = \text{H}$ ] (7.40 g, 22.6 mmol), isoxazoline [compound 13 wherein (QW)= 5-(*N*-*t*-butyl)acetamido  $n = 1$ ,  $R_1 = R_2$

= R<sub>3</sub> = R<sub>4</sub> = R<sub>6</sub> = H] (4.96 g, 58%) was obtained as a crude oil used without purification in the next reaction.

#### Example 10

Preparation of 6-[2-[2-oxo-5-[(*N*-*t*-butyl)acetamido]cyclohexyl]ethyl]-4-oxa-5-azaspiro[2.4]hept-5-ene [compound 14 wherein (QW)= 5-(*N*-*t*-butyl)acetamido n = 1, R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = R<sub>6</sub> = H].

Crude isoxazoline 13 [wherein (QW)= 5-(*N*-*t*-butyl)acetamido n = 1, R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = R<sub>6</sub> = H] (4.92 g, 13.1 mmol) was dissolved in acetone (150 mL) and H<sub>2</sub>SO<sub>4</sub> (1.7 M solution in acetone, 9.8 mL) was slowly added, under vigorous stirring, at room temperature. When the reaction was complete, Na<sub>2</sub>CO<sub>3</sub> was added up to pH 7; after filtration and evaporation of the solvent, crude 14 was obtained. This was purified by chromatography, eluting with CH<sub>2</sub>Cl<sub>2</sub>-MeOH, 60:1 and then 20:1 (R<sub>f</sub> 0.28), affording pure 14 as an oil [compound 14 wherein (QW)= 5-(*N*-*t*-butyl)acetamido n = 1, R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = R<sub>6</sub> = H] (1.45 g, 33%) as a mixture of *cis* and *trans* isomers.

#### Example 11

Preparation of 2,3,5,6,7,8,9,10-octahydro-(1*H*)-8-(*N*-*t*-Butyl)acetamido-benzo[c]quinolizin-3-one [compound 1 wherein (QW)= 8-(*N*-*t*-butyl)acetamido n = 1, R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = R<sub>6</sub> = H and h = double bond] and 2,3,5,6,7,8,9,10-octahydro-(1*H*)-8-(*N*-*t*-Butyl)acetamido-benzo[c]quinolizin-3-one [compound 1 wherein (QW)= 8-(*N*-*t*-butyl)acetamido n = 1, R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = R<sub>6</sub> = H and i = double bond].

A solution of isoxazoline [compound 14 wherein (QW)= 5-(*N*-*t*-butyl)acetamido n = 1, R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = R<sub>6</sub> = H] (947 mg, 2.83 mmol) in DMF (109 mL) was heated under reflux for 3 h. After distillation under reduced pressure of the solvent, a crude oil containing a mixture of rearrangement products was obtained. Chromatographic separation (CH<sub>2</sub>Cl<sub>2</sub>-MeOH, 25:1, 1 % NH<sub>3</sub>) afforded pure 1 (161 mg, 18%, R<sub>f</sub> 0.32, oil) as 10:1 mixture of the two isomers having the double bond in position h or i respectively.

Example 12

Preparation of (+/-)(4a $\alpha$ ,6a $\beta$ ,10a $\alpha$ )-3,4,5,6,6a,7,8,9,10,10a-Decahydro-(4aH)-benzo[c]quinolizin-3-one [compound 1 wherein (QW)<sub>n</sub> = H, R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = R<sub>6</sub> = H and a = double bond ].

5 and (+/-)(4a $\beta$ ,6a $\beta$ ,10a $\alpha$ )-3,4,5,6,6a,7,8,9,10,10a-Decahydro-(4aH)-benzo[c]quinolizin-3-one [compound 1 wherein (QW)<sub>n</sub> = H, R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = R<sub>6</sub> = H and a = double bond]

The (+/-) *trans*-fused *N*-Boc-amide 5, [wherein (QW)<sub>n</sub> = H, R<sub>3</sub> = R<sub>4</sub> = H ] prepared according to known methods, was reduced to compound 6 [wherein (QW)<sub>n</sub> = H, R<sub>3</sub> = R<sub>4</sub> = H ] according to the following procedure : A solution of 5, (4.1 mmol in 12 mL of THF) was cooled to -78°C, and a 1 M solution of LiEt<sub>3</sub>BH in THF (8.2 mL) was slowly added. After 15 min of stirring at -78°C, 2 N HCl in anhydrous EtOH was added dropwise until pH 3.5-4 was reached, immediately followed by addition of 18 mL of ethanol. The mixture was left to warm at 0 °C and after 30 min was diluted with CH<sub>2</sub>Cl<sub>2</sub>. After the usual work-up the product was purified by flash-column chromatography and obtained in 80% yield as a sticky oil.

To a solution of compound 6 [wherein (QW)<sub>n</sub> = H, R<sub>3</sub> = R<sub>4</sub> = H ] (500 mg, 1.76 mmol in 10 mL of CH<sub>2</sub>Cl<sub>2</sub>) at 0°C were added dropwise 1-methoxy-3-trimethylsilyloxy-1,3-butadiene [compound 8, wherein R<sub>1</sub> = MeO, R<sub>2</sub> = H, R<sub>6</sub> = H] (608 mg, 3.53 mmol), NEt<sub>3</sub> (0.5 mL, 3.53 mmol) and TMSOTf (4.4 mmol, 0.85 mL), the mixture was left to warm to r.t. under stirring for 30 min. Then the mixture was treated with NaHCO<sub>3</sub> (satd) for 24 under stirring. Usual work-up and purification by flash column chromatography afforded the 4ab isomer (+/-) (4a $\beta$ ,6a $\beta$ ,10a $\alpha$ )-3,4,5,6,6a,7,8,9,10,10a-decahydro-(4aH)-benzo[c]quinolizin-3-one [compound 1 wherein (QW)<sub>n</sub> = H, R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = R<sub>6</sub> = H and a = double bond] in 20% yield as an oil

The preparation of 4a $\alpha$  isomer was done as follows :

To a solution of compound 6 [wherein (QW)<sub>n</sub> = H, R<sub>3</sub> = R<sub>4</sub> = H ] (200 mg, 0.71 mmol in 5 mL of CH<sub>2</sub>Cl<sub>2</sub>) and 1-methoxy-3-trimethylsilyloxy-1,3-butadiene [compound 8, wherein R<sub>1</sub> = MeO, R<sub>2</sub> = H, R<sub>6</sub> = H] (244 mg, 1.42 mmol), at 0°C was added dropwise TiCl<sub>4</sub> (0.155 mL, of a 2M solution in CH<sub>2</sub>Cl<sub>2</sub>) and the

mixture was left to warm to r.t. under stirring for 1 h. Then the mixture was treated with  $\text{NaHCO}_3$  (satd) for 30 min under stirring. Usual work-up and purification by flash column chromatography afforded the 4aa isomer (+/-) (4a $\alpha$ ,6a $\beta$ ,10a $\alpha$ )-3,4,5,6,6a,7,8,9,10,10a-decahydro-(4aH)-benzo[c]quinolizin-3-one [compound 1 wherein (QW)<sub>n</sub> = H, R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = R<sub>6</sub> = H and a = double bond] in 16% yield as oil.

#### Activity Test

The inhibition potency of the prepared compounds in respect of the iso-enzymes 1 and 2 of 5 $\alpha$ -reductase was determined using cellular systems (for example CHO cells) expressing human iso-enzymes 2 and 1. The samples are incubated in the presence of testosterone labelled with tritium and thereafter the quantity of labelled dihydrotestosterone formed in the absence and in the presence of the inhibitor is measured. The compounds showed high inhibiting power of 5 $\alpha$ -reductase enzyme (in particular of iso-enzyme 1) with an inhibition higher than 50% at the concentration of 10 - 100 nM.

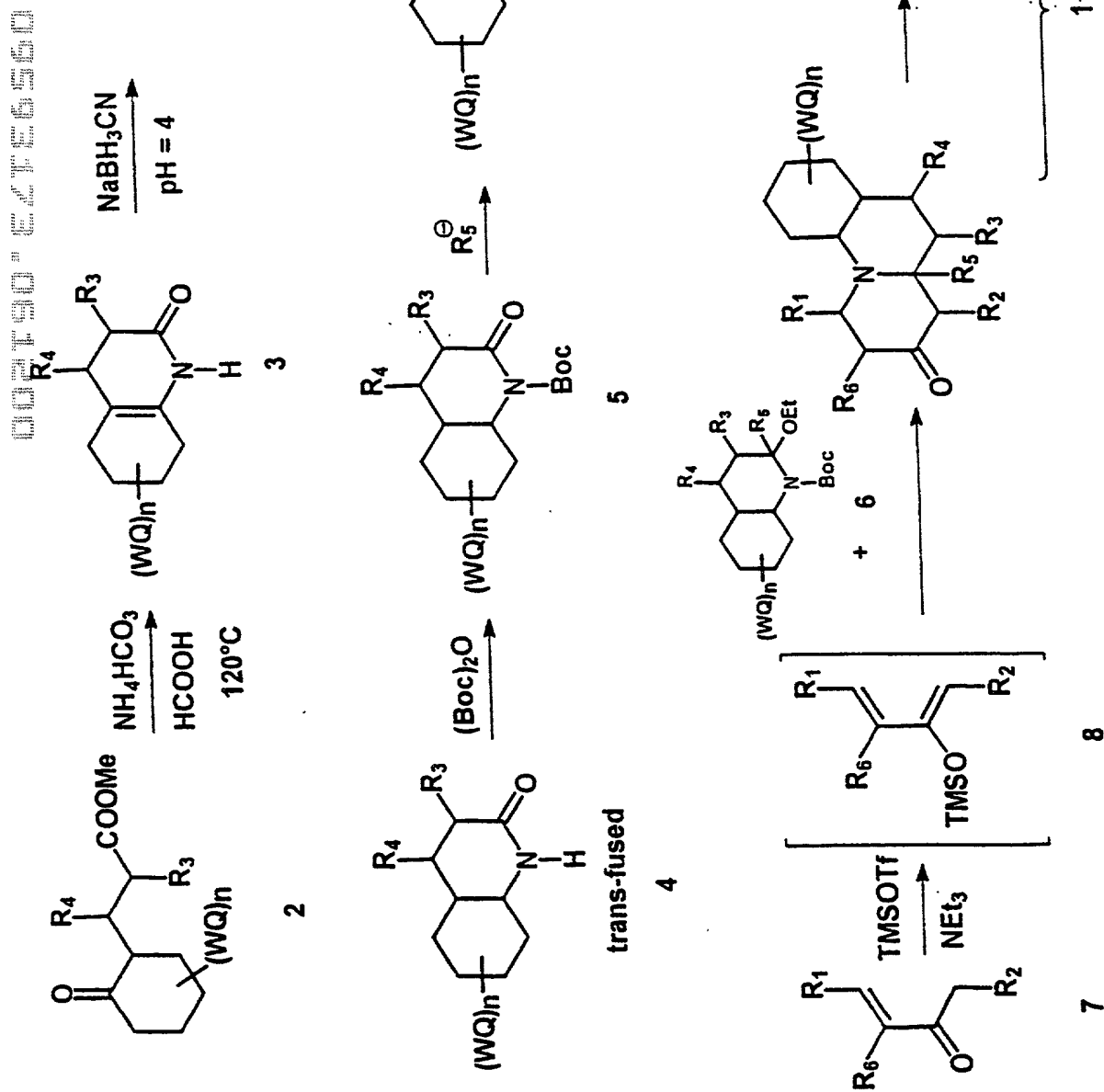
For example the 10:1 mixture of 2,3,5,6,7,8,9,10-octahydro-(1H)-benzo[c]quinolizin-3-one [compound 1 wherein (QW)<sub>n</sub> = H, R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = R<sub>6</sub> = H and h = double bond] and 2,3,5,6,6a,7,8,9-octahydro-(3H)-benzo[c]quinolizin-3-one [compound 1 wherein (QW)<sub>n</sub> = H, R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = R<sub>6</sub> = H and i = double bond], prepared according the example 6, was as selective inhibitor towards type 1 isoenzyme, having an IC<sub>50</sub> value of 58 nM, whereas the IC<sub>50</sub> towards the type 2 isoenzyme was not determinable.

For the therapeutical administration the compounds according to the invention are prepared in the form of pharmaceutical compositions containing the active principle and the organic or inorganic excipients suitable for the oral, parenteral or topic administration of the compositions. The pharmaceutical compositions can therefore be in the solid form (dragees, suppositories, creams, ointments), liquid form (solutions, suspensions, emulsions) and can possibly contain the stabilizers, conservatives, humectants, emulsifier, buffers or salts used for equilibrating the osmotic pressure which are commonly used in the art. Generally the administration of the compounds is performed according to the

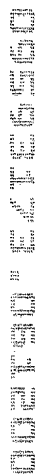


[illegible]

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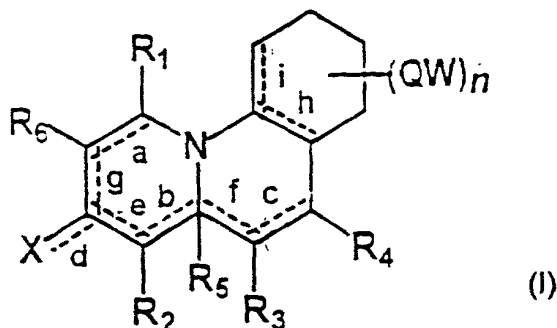


Scheme 1

[illegible]

## Claims

1. Fully and partially reduced benzo[c]-quinolizine compounds of formula (I)



wherein:

$R_1, R_2, R_3, R_4, R_6$ , same or different, are chosen in the group consisting of: H,  $C_{1-8}$ alkyl,  $C_{2-8}$ alkenyl,  $C_{2-8}$ alkynyl, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, norbornane, canphane, adamantane, phenyl, biphenyl, naphthyl, saturated or aromatic heterocycle containing one or more N atoms, halogen, CN, azide,  $NRR'$ ,  $C_{1-8}$ alkylamino, arylamino,  $C_{1-8}$ alkyloxy, aryloxy, COOR, CONRR',  $C(=O)R$ , wherein R and R', same or different, are chosen in the group consisting of: H,  $C_{1-8}$ alkyl, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, norbornane, canphane, adamantane, phenyl, biphenyl, naphthyl, saturated or aromatic heterocycle containing one or more N atoms, phenyl-, biphenyl-, naphthyl- $C_{1-8}$ alkyl;

$R_5$  is chosen in the group consisting of: H,  $C_{1-8}$ alkyl,  $C_{1-8}$ alkyl-phenyl, -biphenyl, -naphthyl, COOR, CN, , phenyl, biphenyl, naphthyl, saturated or aromatic heterocycle containing one or more N atoms,  $C_{1-8}$ alkyl-saturated or aromatic heterocycle containing one or more N atoms;  $C_{1-8}$ alkyl-saturated or aromatic heterocycle containing one or more N atoms -ribose-phosphate

X is chosen in the group consisting of: O,  $C(=O)R$ , COOR,  $NO_2$ , CONR'R wherein R and R' are as above defined;

Q is chosen in the group consisting of: simple bond,  $C_{1-8}$ alkyl,  $C_{2-8}$ alkenyl,  $C_{2-8}$ alkynyl, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, norbornane, canphane, adamantane, CO, CONR, NR, wherein R is as above defined;

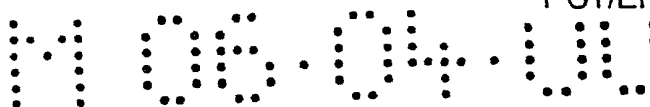
W is chosen in the group consisting of: H,  $C_{1-8}$ alkyl,  $C_{2-8}$ alkenyl,  $C_{2-8}$ alkynyl, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane,

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cyclooctane, norbornane, canphane, adamantane, trifluoromethyl, C<sub>1-8</sub>alkoxy, C<sub>1-8</sub> alkoxy-C<sub>1-8</sub>alkyl, phenyl-, biphenyl-, naphtyl-C<sub>1-8</sub>alkyl, phenyl, biphenyl, naphtyl, phenyloxy, biphenyloxy, naphtyloxy, phenylamino, biphenylamino, naphtylamino, C<sub>1-8</sub>alkylcarbonyl, phenylcarbonyl, biphenylcarbonyl, naphtylcarbonyl, phenylcarboxyl, biphenylcarboxyl, naphtylcarboxyl, phenylcarboxamide, biphenylcarboxamide, naphtylcarboxamide, halogen, CN, NRR', C<sub>1-8</sub>alkylamino, saturated or aromatic heterocycle containing one or more N atoms wherein the groups alkyl, alkenyl, alkynyl, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, norbornane, canphane, adamantane, phenyl, biphenyl, naphtyl, saturated or aromatic heterocycle containing one or more N atoms, can be substituted; n is an integer comprised between 1 and 4;

the symbol — means that the corresponding bonds a, b, c, d e, f, g, h and i can be a simple or a double bond; with the proviso that when b or f are a double bond then the group R<sub>s</sub> is absent;



their pharmaceutically acceptable salts and esters.

2. Benzo[c]-quinolizine compounds of formula (I) according to Claim 1, wherein

$R_5 = H, C_{1-8}$ alkyl-phenyl, -biphenyl, -naphthyl, COOR, CN, phenyl, biphenyl, naphthyl, saturated or aromatic heterocycle containing one or more N atoms,  $C_{1-8}$ alkyl-saturated or aromatic heterocycle containing one or more N atoms; or a group  $C_{1-8}$ alkyl-saturated or aromatic heterocycle containing one or more N atoms -ribose-phosphate

$X = O, COOH$

$Q =$  simple bond, CO, CONR, NR (wherein R is as above defined)  $W = H, F, Cl, Br, Me, t$ -butyl,  $C_{1-8}$ alkoxy, 2,5-dimethylhexyl, trifluoromethyl, 2,5-(di-trifluoromethyl)-phenyl, 4-methoxy-phenyl, 4-fluoro-phenyl, phenyl, phenyl- $C_{1-8}$ alkyl,  $C_{1-8}$ alkylcarbonyl, phenylcarbonyl.

$n = 1$  and 2

$R_1, R_2, R_3, R_4, R_6 = H, Me, CN, phenyl, COOR, CONRR'$  (wherein R and R' are as above defined).

3. Benzo[c]-quinolizine compounds according to Claim 1 of formula :

2,3,4,4a,5,6,6a,7,8,9,10,10a-dodecahydro-(1*H*)-benzo[c]quinolizin-3-one;

8-chloro-2,3,4,4a,5,6,6a,7,8,9,10,10a-dodecahydro-(1*H*)-benzo[c]quinolizin-3-one;

2,3,4,4a,5,6,6a,7,8,9,10,10a-dodecahydro-8-methyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,4,4a,5,6,6a,7,8,9,10,10a-dodecahydro-4-methyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,4,4a,5,6,6a,7,8,9,10,10a-dodecahydro-1-methyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-(1*H*)-benzo[c]quinolizin-3-one;

8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-8-methyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-(1*H*)-benzo[c]quinolizin-3-one;

(4a $\alpha$ , 6a $\beta$ , 10a $\alpha$ )-3,4,5,6,6a,7,8,9,10,10a-decahydro-(4a*H*)benzo[c]quinolizin-3-one;

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(4a $\beta$ , 6a $\beta$ , 10a $\alpha$ )-3,4,5,6,6a,7,8,9,10,10a-decahydro-(4a*H*)benzo[c]quinoliz-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-(4a*H*)-benzo[c]quinolizin-3-one;

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8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-(4a*H*)-benzo[c]quinolizin-3-one;  
3,4,5,6,6a,7,8,9,10,10a-decahydro-8-methyl-(4a*H*)-benzo[c]quinolizin-3-one;  
3,4,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-(4a*H*)-benzo[c]quinolizin-3-one;  
5 3,4,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-(4a*H*)-benzo[c]quinolizin-3-one;  
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-(1*H*)-benzo[c]quinolizin-3-one;  
2,3,5,6,6a,7,8,9,10,10a-decahydro-4,8-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;  
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-(1*H*)-benzo[c]quinolizin-3-one;  
10 2,3,5,6,6a,7,8,9,10,10a-decahydro-1,4-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;  
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-(4a*H*)-benzo[c]quinolizin-3-one;  
3,4,5,6,6a,7,8,9,10,10a-decahydro-4,8-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;  
15 8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-(4a*H*)-benzo[c]quinolizin-3-one;  
3,4,5,6,6a,7,8,9,10,10a-decahydro-1,8-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;  
20 2,3,5,6,6a,7,8,9,10,10a-decahydro-5-methyl-(1*H*)-benzo[c]quinolizin-3-one;  
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-5-methyl-(1*H*)-benzo[c]quinolizin-3-one;  
2,3,5,6,6a,7,8,9,10,10a-decahydro-5,8-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;  
2,3,5,6,6a,7,8,9,10,10a-decahydro-4,5-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;  
25 2,3,5,6,6a,7,8,9,10,10a-decahydro-1,5-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;  
3,4,5,6,6a,7,8,9,10,10a-decahydro-5-methyl-(4a*H*)-benzo[c]quinolizin-3-one;  
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-5-methyl-(4a*H*)-benzo[c]quinolizin-3-one;  
3,4,5,6,6a,7,8,9,10,10a-decahydro-5,8-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;  
30 one;  
3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;  
one;



3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-4,5-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-4,5,8-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;

8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-1,5-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-1,4,5-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;

8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5,8-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5,8-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-6-methyl-(1*H*)-benzo[c]quinolizin-3-one;

8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-6-methyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-6,8-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-4,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-1,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-6-methyl-(4a*H*)-benzo[c]quinolizin-3-one;

8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-6-methyl-(4a*H*)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-6,8-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-4,6-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-1,6-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-4,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

5 2,3,5,6,6a,7,8,9,10,10a-decahydro-4,6,8-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;

8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-1,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

10 2,3,5,6,6a,7,8,9,10,10a-decahydro-1,4,6-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;

8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-4,6-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-4,6,8-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

15 8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-1,6-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-1,6,8-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-5,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

20 8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-5,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-5,6,8-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;

25 2,3,5,6,6a,7,8,9,10,10a-decahydro-4,5,6-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-1,5,6-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-5,6-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

30 8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-5,6-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-5,6,8-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5,6-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

5 3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5,6-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-4,5,6-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;

10 2,3,5,6,6a,7,8,9,10,10a-decahydro-4,5,6,8-tetramethyl-(1*H*)-benzo[c]quinolizin-3-one;

8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-1,5,6-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-1,4,5,6-tetramethyl-(1*H*)-benzo[c]quinolizin-3-one;

15 8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5,6-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5,6,8-tetramethyl-(4a*H*)-benzo[c]quinolizin-3-one;

20 8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5,6-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5,6,8-tetramethyl-(4a*H*)-benzo[c]quinolizin-3-one;

5,6,6a,7,8,9,10,10a-octahydro-(3*H*)-benzo[c]quinolizin-3-one;

8-chloro-5,6,6a,7,8,9,10,10a-octahydro-(3*H*)-benzo[c]quinolizin-3-one;

25 5,6,6a,7,8,9,10,10a-octahydro-8-methyl-(3*H*)-benzo[c]quinolizin-3-one;

5,6,6a,7,8,9,10,10a-octahydro-4-methyl-(3*H*)-benzo[c]quinolizin-3-one;

8-chloro-5,6,6a,7,8,9,10,10a-octahydro-4-methyl-(3*H*)-benzo[c]quinolizin-3-one;

5,6,6a,7,8,9,10,10a-octahydro-4,8-dimethyl-(3*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,7,8,9,10-octahydro-(1*H*)-benzo[c]quinolizin-3-one;

30 8-chloro-2,3,5,6,7,8,9,10-octahydro-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,7,8,9,10-octahydro-8-methyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9-octahydro-(1*H*)-benzo[c]quinolizin-3-one;

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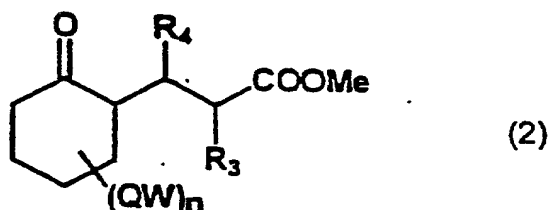
8-chloro-2,3,5,6,6a,7,8,9-octahydro-(1*H*)-benzo[c]quinolizin-3-one;  
 2,3,5,6,6a,7,8,9-octahydro-8-methyl-(1*H*)-benzo[c]quinolizin-3-one;  
 4a-benzyl-3,4,5,6,6a,7,8,9,10,10a-decahydro-(4a*H*)-benzo[c]quinolizin-3-one;  
 4a-benzyl-8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-(4a*H*)-

- 5 benzo[c]quinolizin-3-one;  
 4a-benzyl-3,4,5,6,6a,7,8,9,10,10a-decahydro-8-methyl-(4a*H*)-  
 benzo[c]quinolizin-3-one;  
 4a-benzyl-3,4,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-(4a*H*)-  
 benzo[c]quinolizin-3-one;  
 10 4a-benzyl-3,4,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-(4a*H*)-  
 benzo[c]quinolizin-3-one;  
 3,4,5,6,6a,7,8,9,10,10a-decahydro-4a-(4-pyridyl)methyl-(4a*H*)-  
 benzo[c]quinolizin-3-one;  
 8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-4a-(4-pyridyl)methyl-(4a*H*)-  
 15 benzo[c]quinolizin-3-one;  
 3,4,5,6,6a,7,8,9,10,10a-decahydro-8-methyl-4a-(4-pyridyl)methyl-(4a*H*)-  
 benzo[c]quinolizin-3-one;  
 3,4,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-4a-(4-pyridyl)methyl-(4a*H*)-  
 benzo[c]quinolizin-3-one;  
 20 3,4,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-4a-(4-pyridyl)methyl-(4a*H*)-  
 benzo[c]quinolizin-3-one;

4. Process for the preparation of compounds according to any of claims 1-3  
 wherein:

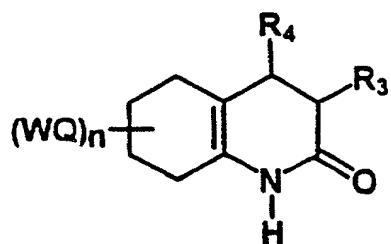
the ester-group of a compound of formula (2)

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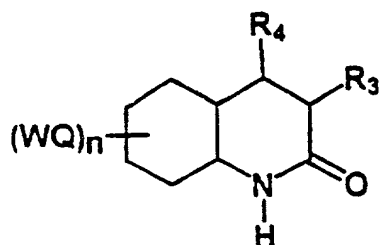
- 30 (wherein  $R_3$ ,  $R_4$  and  $(WQ)_n$  are as defined in Claim 1)  
 is cyclized to enamide (3)

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(3)

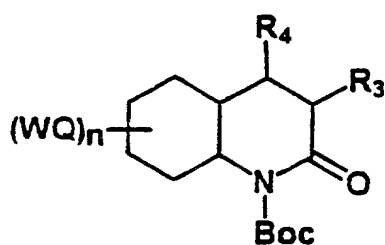
(wherein R<sub>3</sub>, R<sub>4</sub> and (WQ)<sub>n</sub> are as defined in Claim 1)  
which is reduced to the amide (4)



(4)

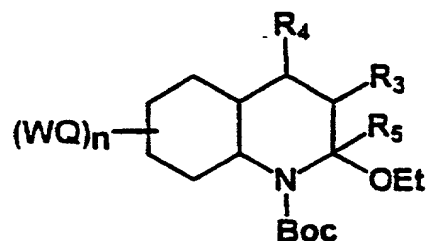
(wherein R<sub>3</sub>, R<sub>4</sub> and (WQ)<sub>n</sub> are as defined in Claim 1)

which is protected with a protecting group Boc to give the compound (5)



(5)

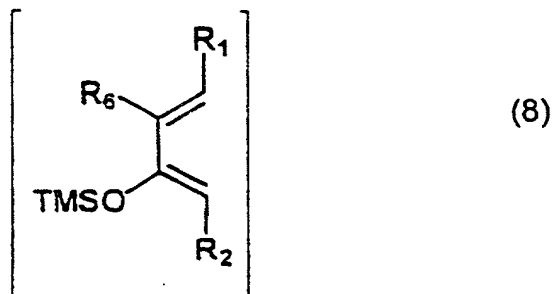
(wherein R<sub>3</sub>, R<sub>4</sub> and (WQ)<sub>n</sub> are as defined in Claim 1)  
which is reduced to compound (6)



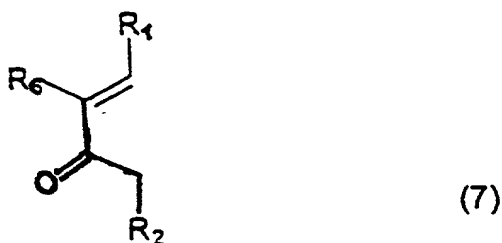
(6)

30

(wherein  $R_3$ ,  $R_4$ ,  $R_5$  and  $(WQ)_n$  are as defined in Claim 1)  
and compound (6) is reacted with a silylether (8)



(wherein  $R_1$ ,  $R_2$  and  $R_6$  are as defined in Claim 1)  
prepared "in situ" by reacting a vinyl-ketone (7)



(wherein  $R_1$ ,  $R_2$ ,  $R_6$  are as above defined) with a silylating agent as  
trimethylsilyltrifluorometansulphonic anhydride (TMSOTf) and are finally  
hydrolyzed, for example with sodium hydrogencarbonate, to give the final  
compound of formula (I) wherein  $X = O$ .

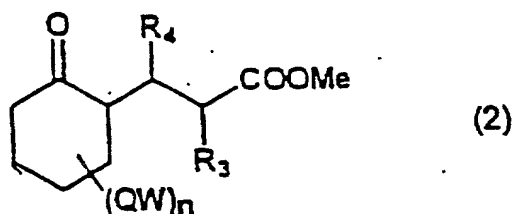
5. Process according to claim 4 wherein the possible introduction of the double  
bonds in position a or b is performed by reaction of dichlorodicianoquinone  
(DDQ) with the corresponding silylenolethers or by oxidation with quicksilver  
acetate of the saturated compound obtained as claimed above and the possible  
transformation of the group X is performed via the corresponding enoltriflates  
and following carbonylation in the presence of palladium diacetate,  
triphenylphosphine and the suitable nucleophilic reagent.

6. Process according to Claim 4 wherein the reaction between the compound  
(6) and the silylether (8) is performed in the presence of  $TiCl_4$ .

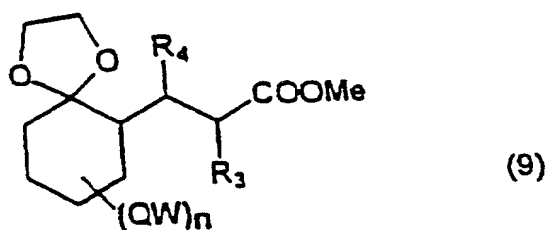
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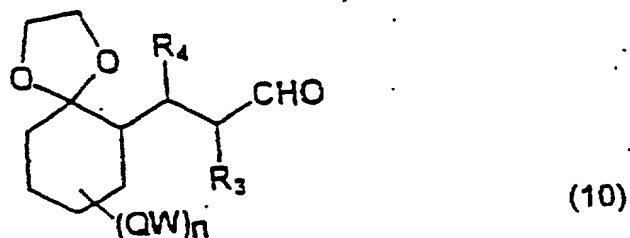
7. Process according to Claim 4 wherein the reaction between compound (6) and the silylether (8) is performed in the presence of TTMSOTf.
8. Process for the preparation of a compound of formula (I) according to any of claims 1-3, wherein:
- 5 the carbonyl group of a compound of formula (2)



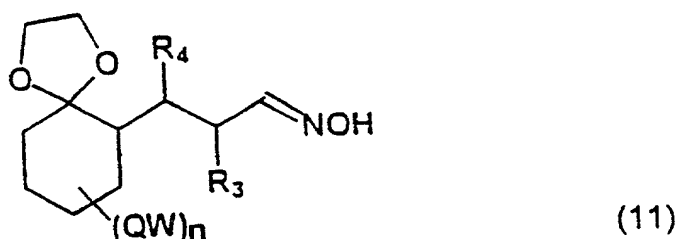
(wherein  $R_3$ ,  $R_4$ , QW and  $n$  are as above defined) is protected as a ketal to give a compound (9)



- 25 (wherein  $R_3$ ,  $R_4$ , QW and  $n$  are as above defined) which is reduced to the corresponding aldehyde (10)



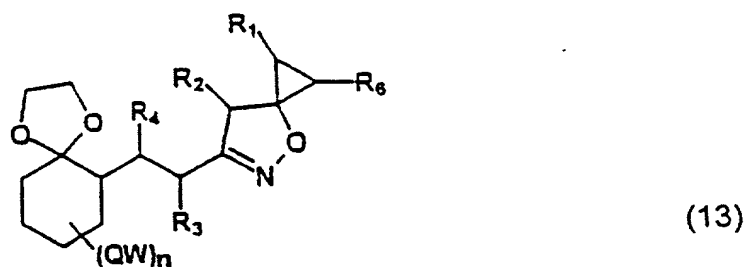
(wherein  $R_3$ ,  $R_4$ , QW and  $n$  are as above defined) with DIBAL, and such  
 5 aldehyde is transformed into the oxime (11)



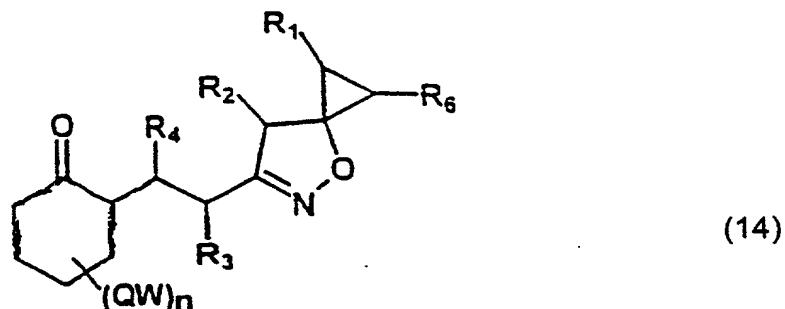
(wherein  $R_3$ ,  $R_4$ , QW and  $n$  are as above defined) which is reacted with a  
 methylenecyclopropane derivative (12)



(wherein  $R_1$ ,  $R_2$  and  $R_6$  are as above defined) to give the isoxazoline (13)



(wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_6$ , QW and  $n$  are as above defined) which is  
 deprotected to the corresponding isoxazoline (14)

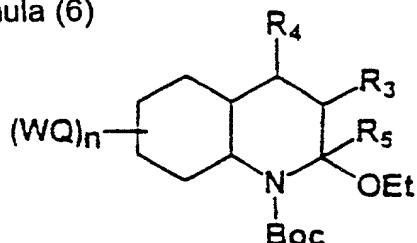




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(wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_6$ , QW and  $n$  are as above defined) which is rearranged to the final product of formula (I) wherein  $X = O$ ,  $i$  or  $h$  is a double bond and the other substituents are as above defined.

9. Compound of formula (6)



(6)

wherein W, Q,  $n$ ,  $R_3$ ,  $R_4$ ,  $R_5$  are as defined in claim 1

10. Pharmaceutical composition wherein the active principle is a compound of formula (I) according to Claim 1 or mixtures thereof in combination with the suitable pharmaceutical acceptable excipients.

11. Pharmaceutical composition according to Claim 10 for use in the inhibition of the  $5\alpha R$ -I and/or  $5\alpha R$ -II iso-enzymes.

12. Pharmaceutical composition according to claims 10 and 11 in the form suitable for topic use.

13. Method for the treatment of pathologies related to  $5\alpha$ -reductase enzymes by administration to the patient of a pharmaceutically active amount of a pharmaceutical composition according to Claims 10.

14. Method according to claim 13 wherein the treated pathologies are acne, baldness, prostatic cancer and prostatic hypertrophy in men and hirsutism in women.

15. Use of compounds of formula (I) according to claim 1 as inhibitors of steroid  $5\alpha$ -reductase enzymes in plants.

16. Agricultural compositions for regulating the plant growth containing as active principle a compound of formula (I) according to Claim 1 or mixtures thereof possibly in combination with the additives commonly used in agriculture for this purposes.

17. Process for plant growth regulation wherein an effective quantity of a composition according to Claim 16 is distributed on the seeds and/or on the plants to treat.